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DOCKET NO. ORT-1236

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Zhang et al.

Serial No.: 09/603,231 Art Unit: 1634

Filed : June 26, 2000 Examiner: Chakrabarti, Arun K.

For : NOVEL INDOLE PEPTIDOMIMETICS AS THROMBIN RECEPTOR ANTAGONISTS

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Mail Stop Appeal, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on

August 26, 2003

(Date)

Hal B. Woodrow

Name of applicant, assignee, or Registered Representative

Hal Brent Woodrow

(Signature)

August 26, 2003

(Date of Signature)

AUTHORIZATION TO CHARGE DEPOSIT ACCOUNT

Mail Stop Appeal
Commissioner for Patents
P.O. Box 1450
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Dear Sir:

Attached is an Appeal Brief for the above-captioned patent application.

Please charge Deposit Account No. 10-0750/ORT1236/HBW in the name of Johnson & Johnson in the amount of $320.00, representing the cost of filing a Brief on Appeal in the above-captioned matter.

The Commissioner is hereby authorized to charge any additional fees which may be required to Account No. 10-0750/ORT1236/HBW. This Authorization is being submitted in triplicate.

Respectfully submitted,

Hal Brent Woodrow

Hal B. Woodrow
Attorney for Applicant(s)
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DATED: August 26, 2003

ORT-1236

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(Name of applicant, assignee, or Registered Representative)

Hal Brent Woodrow
(Signature)

August 26, 2003
(Date of Signature)

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPELLANT'S BRIEF

Appellants respectfully request the Board of Patent Appeals and Interferences reverse the Final Rejection of claims 1-8, 10 and 11 and direct the allowance of said claims.

1. Real Party in Interest

The real party in interest is the assignee, Ortho-McNeil Pharmaceutical, Inc., a Delaware corporation, (and subsidiary of Johnson & Johnson) and COR Therapeutics Inc. (which has been acquired by Millennium Pharmaceutical).

2. Related Appeals and Interferences

There are no related appeals or interferences.

3. Status of the Claims

Claims 1-24 were original present. Claims 9 and 12-24 were subject to a restriction requirement and withdrawn from consideration. Pending claim 1-8 and 10-11 and were finally rejected in the Office Action dated September 20, 2002. Claims have been finally rejected under 35 U.S.C. § 103 as being unpatentable over Forbes (WO 93/18026) and Hoekstra (U.S. Patent 6,017,890).

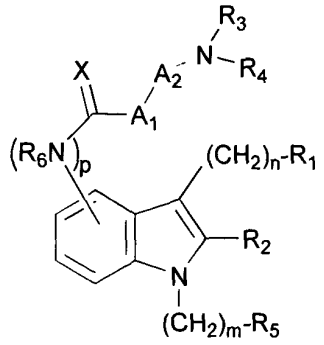
4. Status of Amendments

The first Amendment submitted after Final Rejection was considered. See Advisory Action of April 8, 2003.

5. Summary of the Invention

The invention that is being claimed is a compound of the formula (I).

1. A compound of the following formula (I):



(I)

wherein:

A_1 and A_2 are each independently a D- or L-amino acid selected from the group consisting of alanine, β-alanine, arginine, homoarginine, cyclohexylalanine, citrulline, cysteine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl), 2,4-diaminobutyric acid (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, amidino, or MeC(NH)-), 2,3-diaminopropionic acid (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, amidino, or MeC(NH)-), glutamine, glycine, indanylglycine, lysine (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, MeC(NH)-), valine, methionine, proline, serine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl), homoserine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl), tetrahydroisoquinoline-3-COOH, threonine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl), ornithine (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, MeC(NH)-), and an unsubstituted or substituted aromatic amino acid selected from the group consisting of phenylalanine, heteroarylalanine, naphthylalanine, homophenylalanine, histidine, tryptophan, tyrosine, arylglycine, heteroarylglycine, aryl-β-alanine, and heteroaryl-β-alanine wherein the substituents on the aromatic amino acid are independently selected from one or more of halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, C_1-C_4 alkoxycarbonyl, amino, amidino, guanidino,

fluorinated C_1-C_4 alkyl, fluorinated C_1-C_4 alkoxy, C_1-C_4 alkylsulfonyl, C_1-C_4 alkylcarbonyl, cyano, aryl, heteroaryl, arC_1-C_4 alkyl, C_2-C_4 alkenyl, alkynyl, or nitro;

R_1 is selected from amino, C_1-C_8 alkylamino, C_1-C_8 dialkylamino, arylamino, arC_1-C_8 alkylamino, C_3-C_8 cycloalkylamino, heteroalkylC_1-C_8 alkylamino, heteroalkylC_1-C_8 alkyl-N-methylamino, C_1-C_8 dialkylaminoC_1-C_8 alkylamino, -N(C_1-C_8alkyl)-C_1-C_8 alkyl-N(C_1-C_8alkyl)$_2$, N(C_1-C_8 alkyl)(C_1-C_8 alkenyl), -N(C_1-C_8alkyl)(C_3-C_8cycloalkyl), heteroalkyl or substituted heteroalkyl wherein the substituent on the heteroalkyl is selected from oxo, amino, C_1-C_8 alkoxyC_1-C_8 alkyl, C_1-C_8 alkylamino or C_1-C_8 dialkylamino;

R_2 is selected from hydrogen, halogen, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkenyl, C_1-C_8 alkynyl, arC_1-C_8 alkyl, aryl or heteroaryl;

R_3 and R_4 are each independently selected from hydrogen, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkylC_1-C_8 alkyl, aryl, heteroalkyl, substituted heteroalkyl (wherein the substituent on the heteroalkyl is one or more substituents independently selected from C_1-C_8 alkoxycarbonyl, C_1-C_8 alkyl, or C_1-C_4 alkylcarbonyl), heteroalkylC_1-C_8 alkyl, indanyl, acetamidinoC_1-C_8 alkyl, aminoC_1-C_8 alkyl, C_1-C_8 alkylaminoC_1-C_8 alkyl, C_1-C_8 dialkylaminoC_1-C_8 alkyl, unsubstituted or substituted heteroarylC_1-C_8 alkyl, or unsubstituted or substituted arC_1-C_8 alkyl, wherein the substituent on the aralkyl or heteroarylalkyl group is one or more substituents independently selected from halogen, nitro, amino, C_1-C_8 alkyl, C_1-C_8 alkoxy, hydroxy, cyano, C_1-C_4 alkylcarbonyl, C_1-C_8 alkoxycarbonyl, hydroxyC_1-C_8 alkyl or aminosulfonyl; or

R_3 and R_4, together with the nitrogen to which they are attached, alternatively form an unsubstituted or substituted heteroalkyl group selected from piperidinyl, piperazinyl, morpholinyl or pyrrolidinyl, wherein the substituent is one or more substituents independently selected from C_1-C_8 alkyl C_1-C_8 alkoxycarbonyl or C_1-C_4 alkylcarbonyl;

R_5 is selected from unsubstituted or substituted aryl, arC_1-C_8 alkyl, C_3-C_8 cycloalkyl, or heteroaryl, where the substituents on the aryl, arC_1-C_8 alkyl, cycloalkyl or heteroaryl group are independently selected from one or more of halogen, nitro, amino, cyano, hydroxyalkyl, C_1-C_8 alkyl, C_1-C_8 alkoxy, hydroxy, C_1-C_4 alkylcarbonyl, C_1-C_8 alkoxycarbonyl, fluorinated C_1-C_4 alkyl, fluorinated C_1-C_4 alkoxy or C_1-C_4 alkylsulfonyl;

R_6 is selected from hydrogen or C_1-C_8 alkyl,

X is oxygen or sulfur;

m is an integer selected from 0, 1, 2 or 3;
n is an integer selected from 1 or 2; and
p is an integer selected from 0 or 1;

and pharmaceutically acceptable salts thereof.

6. Issues

I. Whether a prima facie case of obviousness has been established for the rejection of claims 1-8, 10 and 11 under 35 U.S.C. §103.

II. Whether a case of structural obviousness has been established for the rejection of claims 1-8, 10 and 11 under 35 U.S.C. § 103.

7. Grouping of the Claims

For Issue I, claims 1-8, 10 and 11 shall stand or fall together.

For Issue II, claims 1-8, 10 and 11 shall stand or fall together.

8. Arguments

I

The rejection of claims 1-8, 10 and 11 under 35 U.S.C. 103 (a) over Forbes et al. over Hoekstra et al. is submitted to be in error for the reasons argued here in (paraphrasing In re Dembiczak 50 USPQ 1614 (Fed. Cir. 1999)).

'A claimed invention is unpatentable if the differences between it and the prior art "are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a) (Supp. 1998); see Graham v. John Deere Co., 383 U.S. 1, 14, 148 USPQ 459, 465 (1966). The ultimate determination of whether an invention is or is not obvious is a legal conclusion based on underlying factual inquiries including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the prior art; (3) the differences between the claimed invention and the prior art; and (4) objective evidence of nonobviousness. See Graham, 383 U.S. at 17-18, 148 USPQ at 467; Miles Labs, Inc., Inc. v. Shandon Inc., 997 F.2d 870, 877, 27 USPQ2d 1123, 1128 (Fed. Cir. 1993).

The analysis of obviousness must begin with the text of section 103 quoted above, with the phrase "at the time the invention was made." For it is this phrase that guards against entry into the "tempting but forbidden zone of hindsight," see Loctite Corp. v. Ultraseal Ltd., 781 F.2d 861, 873, 228 USPQ 90, 98 (Fed. Cir. 1985), overruled on other grounds by Nobelpharma AB v. Implant Innovations, Inc., 141 F.3d 1059, 46 USPQ2d 1097 (Fed. Cir. 1998), when analyzing the patentability of claims pursuant to that section. Measuring a claimed invention against the standard established by section 103 requires the oft-difficult but critical step of casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided

only by the prior art references and the then-accepted wisdom in the field. See, e.g., W.L. Gore & Assoc., Inc. v. Garlock, Inc., 721 F.2d 1540, 1553, 220 UPSQ 303, 313 (Fed. Cir. 1983).

The Federal Circuit's case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references. See, e.g., C.R. Bard, Inc. v. M3 Sys., Inc., 157 F.3d 1340, 1352, 48 USPQ2d 1225, 1232 (Fed. Cir. 1998) (describing "teaching or suggestion or motivation [to combine]" as an "essential evidentiary component of an obviousness holding"); In re Rouffet, 149 F.3d 1350, 1359, 47 USPQ2d 1453, 1459 (Fed. Cir. 1998) ("the Board must identify specifically . . . the reasons one of ordinary skill in the art would have been motivated to select the references and combine them"); In re Fritch, 972 F.2d 1260, 1265, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992) (examiner can satisfy burden of obviousness in light of combination "only by showing some objective teaching [leading to the combination]"); In re Fine, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988) (evidence of teaching or suggestion "essential" to avoid hindsight); Ashland Oil, Inc. v. Delta Resins & Refractories, Inc., 776 F.2d 281, 297, 227 USPQ 657, 667 (Fed. Cir. 1985) (district court's conclusion of obviousness was error when it "did not elucidate any factual teachings, suggestions or incentives from this prior art that showed the propriety of combination"). See also Graham, 383 U.S. at 18, 148 USPQ at 467 ("strict observance" of factual predicates to obviousness conclusion required). Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight. See, e.g., Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1138, 227 USPQ 543, 547 (Fed. Cir. 1985) ("The invention must be viewed not with the blueprint drawn by the inventor, but in the state of the art that existed at the time."). In this case, it appears that the Examiner has fallen into the hindsight trap.'

Forbes et al. on page 1 of the specification in lines 13 et seq. describes the application as being a new class of compounds that have been found to have $5HT_{1C}$ receptor antagonist activity. $5HT_{1C}$ receptors antagonists are described in Forbes as being potential use for the treatment of CNS disorders such as anxiety, depression, obsessive compulsive disorders, migraine, anorexia, Alzheimers disease, sleep disorders, bulimia, panic attacks, withdrawal from drug abuse and/or schizophrenia. 5-HT1C (5-hydroxytryptamine) is a G protein-coupled serotonin receptor. The $5HT_{1C}$ receptor according to Pompeiano et al. (abstract provided to the examiner) indicates that $5HT_{1C}$ has been renamed the 5-HT2C receptor. The potential medical benefits of 5-HT research is described by Jones et al. (article provided to the examiner). Jones suggests that selective 5HT2C receptor antagonists could have antidepressant properties (see page 557), a role in the treatment of generalized anxiety disorder (page 559) and appetite (page 563).

Forbes et al. does not teach, suggest or disclose that there are any similarity between compounds that would antagonize the 5HT2C receptor and compounds that would antagonize the PAR-1 receptors. There does not appear to be any suggestion or disclosure in Forbes et al. that the compounds described therein have any activity toward the PAR-1 receptor. Forbes also does not suggest or describe modifying the compounds described therein to make the compounds that are claimed by the applicants.

Although Hoekstra et al. is a significant contribution to the art of PAR-1 antagonists, Hoekstra does not teach, suggest or disclose that the compounds described therein are 5HT2C antagonists. Hoekstra et al. also does not teach, suggest or disclose compounds of the structure being claimed in the present invention. Hoekstra et al. also does not teach or suggest that the A1 and A2 portion of the compounds that he claims may be combined with other scaffolds such as those described by Forbes et al. to provide PAR1 antagonists.

The Examiner has asserted that Hoekstra et al. "teach a compound with A1 and A2 which are D- or L- amino acids" in (Column 1, lines 8-35 and Claim 1). See Advisory Action page 2, third paragraph. However, Hoekstra et al. in Column 1, lines 8-35 discusses prior art publications

related to SFLLRN (Ser-Phe-Leu-Leu-Arg-Asn) a six amino acid motif that is involved in PAR1 receptor activation. Claim 1 of Hoekstra et al. defines a chemical structure that is a PAR1 antagonist. Neither the prior art nor Hoekstra suggest or disclose that A1 and A2 can be selectively removed from the SFLLRN motif or the compound of claim 1 and combined with other structures to provide a PAR1 antagonist.

In view of the deficiencies in Forbes et al. and Hoekstra et al., appellants respectfully submit that one of ordinary skill in the art when designing a PAR-1 antagonist would not be motivated to combine part of Forbes 5HT2C compounds with part of Hoekstra's disclosed compounds to form the claimed invention. The documents of record simply do not evidence a suggestion, teaching, or motivation to combine the documents of record. See In re Fine, 837 F.2d 1071, 5 USPQ2d 1596, (Fed. Cir. 1988). There must be a clear and particular showing of this evidence. See, e.g., C.R. Bard, 157 F.3d at 1352, 48 USPQ2d at 1232. Conclusory statements regarding the teaching of multiple references, standing alone, is not "evidence." E.g., McElmurry v. Arkansas Power & Light Co., 995 F.2d 1576, 1578, 27 USPQ2d 1129, 1131 (Fed. Cir. 1993). Therefore, appellants respectfully submit that the Office has not met its burden of establishing a *prima facie* case of obviousness.

The present rejection of the claims is limited to a discussion of the ways that the prior art references can be combined to read on the claimed invention. Yet this analysis fails to demonstrate how the Forbes et al. and Hoekstra et al. references teach or suggest their combination to yield the claimed invention. See Rouffet, 149 F.3d at 1357, 47 USPQ2d at 1459. Appellants respectfully submit that they do not discern any suggestion, teaching, or motivation to combine the prior art references cited against the pending claims. Therefore appellants respectfully submit that the Examiner's conclusion that the present claims are obviousness, as a matter of law, cannot stand. See C.R. Bard, 157 F.3d at 1352, 48 USPQ2d at 1232; Rouffet, 149 F.3d at 1359, 47 USPQ2d at 1459; Fritch, 972 F.2d at 1265, 23 USPQ2d at 1783; Fine, 837 F.2d at 1075, 5 USPQ2d at 1600; Ashland Oil, 776 F.2d at 297, 227 USPQ at 667. Appellants note

the Examiner's citation of In re McLaughlin, 443 F.2d 1392, 170 USPQ 209, however, appellants do not believe the selective hindsight evidenced in the present rejection would pass the test set forth in current case law.

Accordingly appellants respectfully submit that the rejection of claims 1-8, 10 and 11 under 35 U.S.C. 103 (a) over Forbes et al. over Hoekstra et al. is in error and should be reversed.

II

Claims 1-8, 10 and 11 have been rejected under 35 U.S.C. 103 (a) over Forbes et al. and Hoekstra et al. However, appellants respectfully submit that a *prima facie* case of structural obviousness has not been established by the Forbes et al. or Hoekstra et al. taken alone or together.

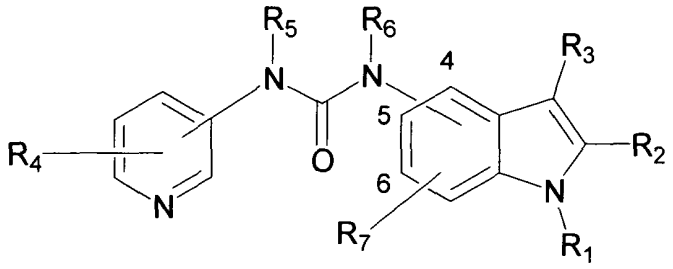
A claimed invention is unpatentable if the differences between it and the prior art "are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a) (Supp. 1998); see Graham v. John Deere Co., 383 U.S. 1, 14, 148 USPQ 459, 465 (1966). The ultimate determination of whether an invention is or is not obvious is a legal conclusion based on underlying factual inquiries including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the prior art; (3) the differences between the claimed invention and the prior art; and (4) objective evidence of nonobviousness. See Graham, 383 U.S. at 17-18, 148 USPQ at 467; Miles Labs, Inc., Inc. v. Shandon Inc., 997 F.2d 870, 877, 27 USPQ2d 1123, 1128 (Fed. Cir. 1993).

In Yamanouchi Pharmaceutical v Merck, 231 F.3d 1339, 1343 56 U.S.P.Q.2d 1641 (Fed. Cir. 2000), reh'g and reh'g en banc denied, (Dec. 14, 2000) the Federal Circuit explained the obviousness standard for chemical compounds as follows:

For a chemical compound, a prima facie case of obviousness requires "structural similarity between claimed and prior art subject matter . . . where the prior art gives reason or motivation to make the claimed compositions." In re Dillon, 919 F.2d 688, 692, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990) (en banc). "[A] reasonable expectation of success, not absolute predictability" supports a conclusion of obviousness. In re Longi, 759 F.2d 887, 896, 225 USPQ 645, 651-52 (Fed. Cir. 1985).

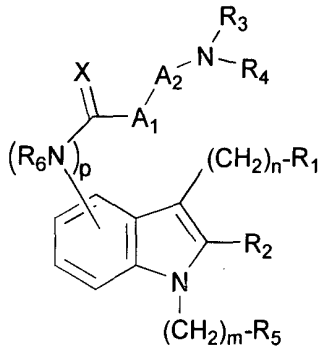
There must be motivation to combine the prior art references to produce the claimed invention. The question in the Yamanouchi dispute was whether one of skill in the art would have found the motivation to combine pieces from one compound in a prior art patent with a piece of another compound in a second prior art patent through a series of manipulations. In Yamanouchi as here the assertion of obviousness was based on a combination of pieces of other compounds followed by further modifications to provide the final compound. The Court set forth three specific requirements that would have to be met for structural obviousness to be proven. First the prior art would have to provide the specific motivation to combine the references (which is lacking here). Second the Court went on to indicate that a reasonable expectation of success in finding active would also have to be expected of the claimed compounds by one of ordinary skill in the art (which does not appear to be present here). Third the Court indicated that the prior art must offer a suggestion to pursue the particular manipulation of parts of the compounds (which also does not exist here).

Assuming for the purpose of this discussion only that Forbes et al. could be properly combined with Hoekstra et al., the rejection of the claimed invention over Forbes et al. over Hoekstra et al. does not satisfy the test for obviousness set forth in Yamanouchi. The Advisory Action has alleged that Forbes et al. Formula I teaches all the limitation of claims 1-8, but devoid of A1 and A2. However, this statement is factually incorrect. Forbes et al. shows a pyridine linked through a urea to an indole in Formula (I).



Formula (I) of Forbes et al.

That structure does not exist in claim 1-8. The appellants' claimed compounds do not provide the same urea pyridine structure.



(Formula I of Appellants' Claimed Compounds)

Thus, Forbes et al. does not meet all the limitations of claims 1-8. Consequently, the addition of A1 and A2 of Hoekstra et al. to Forbes et al. does not provide the compounds of claims 1-8.

Even if one were to ignore the additional pyridine present in Forbes et al., the structure described by Forbes as his pharmaceutically active compound on pages 1 and 2 of the specification still would not provide the same compounds as are being claimed by the appellants. Forbes shows the indole portion of his compound as being substituted with R_1, R_2, and R_3. These substituents are described as hydrogen or C_{1-6} alkyl on page 2, line 1 of Forbes et al. The appellants' claimed compounds on the indole ring claims 1-8 define different substituents being

substituted from the indole ring. For example, R_1 of Forbes et al. corresponds to $(CH_2)_m$-R_5 of the appellants' compound which is defined as:

In claim 1:

R_5 is selected from unsubstituted or substituted aryl, arC_1-C_8 alkyl, C_3-C_8 cycloalkyl, or heteroaryl, where the substituents on the aryl, arC_1-C_8 alkyl, cycloalkyl or heteroaryl group are independently selected from one or more of halogen, nitro, amino, cyano, hydroxyalkyl, C_1-C_8 alkyl, C_1-C_8 alkoxy, hydroxy, C_1-C_4 alkylcarbonyl, C_1-C_8 alkoxycarbonyl, fluorinated C_1-C_4 alkyl, fluorinated C_1-C_4 alkoxy or C_1-C_4 alkylsulfonyl;

In claim 4:

R_5 is selected from cyclohexyl, 2-naphthyl, phenylethyl, 4-fluorophenylethyl, or unsubstituted or substituted phenyl, where the substituents on the phenyl are independently selected from one to two substituents selected from fluorine, chlorine, iodine, methyl, cyano or trifluoromethyl;

Similarly R_3 of Forbes corresponds to $(CH_2)_n$-R_1 of the appellants' compound which is defined to be

In claim 1:

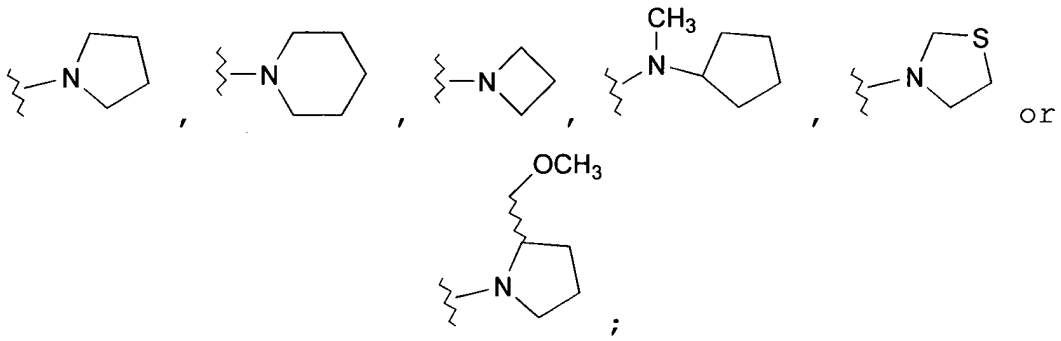
R_1 is selected from amino, C_1-C_8 alkylamino, C_1-C_8 dialkylamino, arylamino, arC_1-C_8 alkylamino, C_3-C_8 cycloalkylamino, heteroalkylC_1-C_8 alkylamino, heteroalkylC_1-C_8 alkyl-N-methylamino, C_1-C_8 dialkylaminoC_1-C_8 alkylamino, -N(C_1-C_8alkyl)-C_1-C_8 alkyl-N(C_1-C_8alkyl)$_2$, N(C_1-C_8 alkyl)(C_1-C_8 alkenyl), -N(C_1-C_8alkyl)(C_3-C_8cycloalkyl), heteroalkyl or substituted heteroalkyl wherein the substituent on the heteroalkyl is selected from oxo, amino, C_1-C_8 alkoxyC_1-C_8 alkyl, C_1-C_8 alkylamino or C_1-C_8 dialkylamino;

In claim 2:

R_1 is selected from amino, C_1-C_6 alkylamino, C_1-C_6 dialkylamino, arylamino, arC_1-C_6 alkylamino, heteroalkylC_1-C_6 alkylamino, -N(C_1-C_6 alkyl)-C_1-C_6 alkyl-N(C_1-C_6 alkyl)$_2$, heteroalkyl or substituted heteroalkyl wherein the substituent on the heteroalkyl is selected from oxo, amino, C_1-C_6 alkoxy C_1-C_6 alkyl, C_1-C_6 alkylamino or C_1-C_6 dialkylamino;

In claim 4:

R_1 is selected from diethylamino, di-(*n*-propyl)amino,



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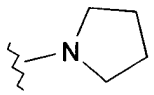
In claim 5:

R_1 is 

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Following the tests set forth in Yamanouchi the first step of the analysis is to determine whether one of sill in the art would have been found motivation to combine the Forbes et al. and Hoekstra et al. references, which as was argued in Issue I is simply not present in the references. The second and third step of the Yamanouchi analysis are to determine whether there is a reasonable expectation of success in finding that activity and for performing the manipulations. As was previously argued, since the Forbes et al. reference is related to a totally different receptor the expectation of finding activity for the PAR1 receptor when combining selected portions of the

Forbes compound with selected portions of the Hoekstra compounds does not provide a reasonable expectation that a pharmaceutically active compound for the PAR1 receptor would be provided. The third step of the Yamanouchi analysis is to determine whether there is a suggestion to pursue the particular manipulation of parts of the compounds. In reviewing the combination Forbes et al and Hoekstra et al. as described above it is clear that the combination does not suggest or disclose the compounds that are being claimed. Therefore, the question is whether the references would suggest pursuing the particular manipulations of parts of the compounds to arrive at the claimed compounds. However, on inspection of Forbes et al. and Hoekstra et al. there is no motivation provided for the combination of these references much less for the modifications of Forbes et al. to remove the pyridine ring and modify the R group extending from the indole ring, nor the selection of A1 and A2 from Hoekstra to add to a modified Forbes compound.

Appellants have taken note that although the rejection has been stated to be based on formula (I) of Forbes et al., it has been suggested that formula IV of Forbes is also being applied against the claimed invention. For example, on page 6 of Paper 12 it is stated that with regard to R_1 and R_3 of Forbes, that the intermediates for R_1 and R_3 of indole portion of Forbes are being used in combination with Hoekstra as the basis of the rejection. To have structural obviousness as was stated in Yamanouchi, there must be a showing of motivation in the prior art for this combination, a reasonable expectation of success and a suggestion to pursue this particular manipulation (the use of an intermediate to form the final active compound). As applicants have previously discussed there is no basis for combining Forbes et al. and Hoekstra et al. Additionally, Forbes does not teach, suggest or disclose that the intermediate portion of the Forbes compound possesses activity. Appellants respectfully submit that one of ordinary skill in the art would not have been motivated to select an inactive intermediates of Forbes et al. compound to modify by the addition of the A1 and A2 components of Hoekstra et al. while removing the pyridine component of Forbes. Similarly one of ordinary skill in the art would not have had a reasonable expectation that such a compound so modified would have pharmaceutical activity. Consequently, appellants submit that the reasonable expectation of success is lacking here. Further, there is ***no basis*** for picking and choosing any

portion of Forbes et al. much less an intermediate of a portion of Forbes to piece together with portions of Hoekstra et al. in an attempt to recreate the present invention. There is also no teaching, suggestion or disclosure in Forbes or Hoekstra that would motivate this course of action. Therefore, appellants' submit that the rejection of claims 1-8, 10 and 11 does not meet the tests Yamanouchi and a *prima facie* case of structural obviousness has not been established for the claimed compound.

Accordingly appellants respectfully submit that the rejection of claims 1-8, 10 and 11 under 35 U.S.C. 103 (a) over Forbes et al. over Hoekstra et al. is in error and should be reversed.

Conclusion

In conclusion, appellants respectfully request that the Board of Patent Appeals and Interferences reverse the Final Rejection of claims 1-8, 10 and 11 over Forbes et al and Hoekstra et al. and direct the allowance of claims 1-8, 10 and 11.

Respectfully submitted,

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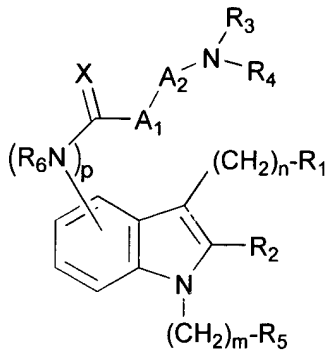
APPENDIX

WHAT IS CLAIMED IS:

1. A compound of the following formula (I):



(I)

wherein:

A_1 and A_2 are each independently a D- or L-amino acid selected from the group consisting of alanine, β-alanine, arginine, homoarginine, cyclohexylalanine, citrulline, cysteine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl), 2,4-diaminobutyric acid (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, amidino, or MeC(NH)-), 2,3-diaminopropionic acid (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, amidino, or MeC(NH)-), glutamine, glycine, indanylglycine, lysine (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, MeC(NH)-), valine, methionine, proline, serine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl), homoserine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl), tetrahydroisoquinoline-3-COOH, threonine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl), ornithine (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, MeC(NH)-), and an unsubstituted or substituted aromatic amino acid selected from the group consisting of

phenylalanine, heteroarylalanine, naphthylalanine, homophenylalanine, histidine, tryptophan, tyrosine, arylglycine, heteroarylglycine, aryl-β-alanine, and heteroaryl-β-alanine wherein the substituents on the aromatic amino acid are independently selected from one or more of halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, C_1-C_4 alkoxycarbonyl, amino, amidino, guanidino, fluorinated C_1-C_4 alkyl, fluorinated C_1-C_4 alkoxy, C_1-C_4 alkylsulfonyl, C_1-C_4 alkylcarbonyl, cyano, aryl, heteroaryl, arC_1-C_4 alkyl, C_2-C_4 alkenyl, alkynyl, or nitro;

R_1 is selected from amino, C_1-C_8 alkylamino, C_1-C_8 dialkylamino, arylamino, arC_1-C_8 alkylamino, C_3-C_8 cycloalkylamino, heteroalkylC_1-C_8 alkylamino, heteroalkylC_1-C_8 alkyl-N-methylamino, C_1-C_8 dialkylaminoC_1-C_8 alkylamino, -N(C_1-C_8alkyl)-C_1-C_8 alkyl-N(C_1-C_8alkyl)$_2$, N(C_1-C_8 alkyl)(C_1-C_8 alkenyl), -N(C_1-C_8alkyl)(C_3-C_8cycloalkyl), heteroalkyl or substituted heteroalkyl wherein the substituent on the heteroalkyl is selected from oxo, amino, C_1-C_8 alkoxyC_1-C_8 alkyl, C_1-C_8 alkylamino or C_1-C_8 dialkylamino;

R_2 is selected from hydrogen, halogen, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkenyl, C_1-C_8 alkynyl, arC_1-C_8 alkyl, aryl or heteroaryl;

R_3 and R_4 are each independently selected from hydrogen, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkylC_1-C_8 alkyl, aryl, heteroalkyl, substituted heteroalkyl (wherein the substituent on the heteroalkyl is one or more substituents independently selected from C_1-C_8 alkoxycarbonyl, C_1-C_8 alkyl, or C_1-C_4 alkylcarbonyl), heteroalkylC_1-C_8 alkyl, indanyl, acetamidinoC_1-C_8 alkyl, aminoC_1-C_8 alkyl, C_1-C_8 alkylaminoC_1-C_8 alkyl, C_1-C_8 dialkylaminoC_1-C_8 alkyl, unsubstituted or substituted heteroarylC_1-C_8 alkyl, or unsubstituted or substituted arC_1-C_8 alkyl, wherein the substituent on the aralkyl or heteroarylalkyl group is one or more substituents independently selected from halogen, nitro, amino, C_1-C_8 alkyl, C_1-C_8 alkoxy, hydroxy, cyano, C_1-C_4 alkylcarbonyl, C_1-C_8 alkoxycarbonyl, hydroxyC_1-C_8 alkyl or aminosulfonyl; or

R_3 and R_4, together with the nitrogen to which they are attached, alternatively form an unsubstituted or substituted heteroalkyl group selected from piperidinyl, piperazinyl, morpholinyl

or pyrrolidinyl, wherein the substituent is one or more substituents independently selected from C_1-C_8 alkyl C_1-C_8 alkoxycarbonyl or C_1-C_4 alkylcarbonyl;

R_5 is selected from unsubstituted or substituted aryl, arC_1-C_8 alkyl, C_3-C_8 cycloalkyl, or heteroaryl, where the substituents on the aryl, arC_1-C_8 alkyl, cycloalkyl or heteroaryl group are independently selected from one or more of halogen, nitro, amino, cyano, hydroxyalkyl, C_1-C_8 alkyl, C_1-C_8 alkoxy, hydroxy, C_1-C_4 alkylcarbonyl, C_1-C_8 alkoxycarbonyl, fluorinated C_1-C_4 alkyl, fluorinated C_1-C_4 alkoxy or C_1-C_4 alkylsulfonyl;

R_6 is selected from hydrogen or C_1-C_8 alkyl,

X is oxygen or sulfur;

m is an integer selected from 0, 1, 2 or 3;
n is an integer selected from 1 or 2; and
p is an integer selected from 0 or 1;

and pharmaceutically acceptable salts thereof.

2. The compound of Claim 1, wherein:

A_1 and A_2 are each independently an L-amino acid selected from the group consisting of alanine, β-alanine, arginine, homoarginine, cyclohexylalanine, citrulline, cysteine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl), 2,4-diaminobutyric acid (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, amidino, or MeC(NH)-), 2,3-diaminopropionic acid (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, amidino, or MeC(NH)-), glutamine, glycine, indanylglycine lysine (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, MeC(NH)-), valine, methionine, proline, serine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl), homoserine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl),

tetrahydroisoquinoline-3-COOH, threonine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl), ornithine (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, MeC(NH)-), and an unsubstituted or substituted aromatic amino acid selected from the group consisting of phenylalanine, heteroarylalanine, naphthylalanine, homophenylalanine, histidine, tryptophan, tyrosine, arylglycine, heteroarylglycine, aryl-β-alanine, and heteroaryl-β-alanine wherein the substituents on the aromatic amino acid are independently selected from one or more of halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, C_1-C_4 alkoxycarbonyl, amino, amidino, guanidino, fluorinated C_1-C_4 alkyl, fluorinated C_1-C_4 alkoxy, C_1-C_4 alkylsulfonyl, C_1-C_4 alkylcarbonyl, cyano, aryl, heteroaryl, arC_1-C_4 alkyl, C_2-C_4 alkenyl, alkynyl, or nitro;

R_1 is selected from amino, C_1-C_6 alkylamino, C_1-C_6 dialkylamino, arylamino, arC_1-C_6 alkylamino, heteroalkylC_1-C_6 alkylamino, -N(C_1-C_6 alkyl)-C_1-C_6 alkyl-N(C_1-C_6 alkyl)$_2$, heteroalkyl or substituted heteroalkyl wherein the substituent on the heteroalkyl is selected from oxo, amino, C_1-C_6 alkoxy C_1-C_6 alkyl, C_1-C_6 alkylamino or C_1-C_6 dialkylamino;

R_2 is selected from hydrogen, halogen or phenyl;

R_3 is selected from hydrogen or C_1-C_6 alkyl;

R_4 is selected from C_1-C_8 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkylC_1-C_6 alkyl, aryl, heteroarylC_1-C_6 alkyl, substituted heteroarylC_1-C_6 alkyl wherein the substituent is C_1-C_4 alkyl, heteroalkyl, heteroalkylC_1-C_6 alkyl, indanyl, acetamidinoC_1-C_6 alkyl, aminoC_1-C_6 alkyl, C_1-C_6 alkylaminoC_1-C_6 alkyl, C_1-C_6 dialkylaminoC_1-C_6 alkyl, arC_1-C_8 alkyl, substituted arC_1-C_8 alkyl wherein the substituent on the aralkyl group is one to five substituents independently selected from halogen, nitro, amino, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxycarbonyl, hydroxyalkyl or aminosulfonyl; or

R_3 and R_4, together with the nitrogen to which they are attached, alternatively form an unsubstituted or substituted heteroalkyl group selected from piperidinyl, piperazinyl or

pyrrolidinyl, wherein the substituent is independently one or two substituents selected from C_1-C_6 alkyl;

R_5 is selected from unsubstituted or substituted aryl, arC_1-C_6 alkyl, C_3-C_6 cycloalkyl or heteroaryl, where the substituents on the aryl, aralkyl, cycloalkyl or heteroaryl group are independently selected from one to three substituents selected from halogen, cyano, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 alkoxycarbonyl, fluorinated C_1-C_4 alkyl, fluorinated C_1-C_4 alkoxy or C_1-C_4 alkylsulfonyl;

R_6 is hydrogen; and

X is oxygen; and

p is 1;

and pharmaceutically acceptable salts thereof.

3. The compound of Claim 2, wherein:

A_1 is an L-amino acid selected from the group consisting of alanine, arginine, cyclohexylalanine, glycine, proline, tetrahydroisoquinoline-3-COOH, and an unsubstituted or substituted aromatic amino acid selected from the group consisting of phenylalanine, naphthylalanine, homophenylalanine, and O-methyl tyrosine, wherein the substituents on the aromatic amino acid are independently one to five substituents selected from halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, C_1-C_4 alkoxycarbonyl, amino, amidino, guanidino, fluorinated C_1-C_4 alkyl, fluorinated C_1-C_4 alkoxy, C_1-C_4 alkylsulfonyl, C_1-C_4 alkylcarbonyl, cyano, aryl, heteroaryl, arC_1-C_4 alkyl, C_2-C_4 alkenyl, alkynyl, or nitro;

A_2 is an L-amino acid selected from the group consisting of alanine, β-alanine, arginine, citrulline, cysteine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl), 2,4-diaminobutyric acid (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, amidino, or MeC(NH)-), 2,3- diaminopropionic acid (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, amidino, or MeC(NH)-), glutamine, glycine, lysine (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, MeC(NH)-), valine, methionine, serine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl), homoserine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl), threonine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl), ornithine (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, MeC(NH)-), and an unsubstituted or substituted aromatic amino acid selected from the group consisting of phenylalanine, heteroarylalanine, and histidine, wherein the substituents of the aromatic amino acid are independently one to five substituents selected from halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, C_1-C_4 alkoxycarbonyl, amino, amidino, guanidino, fluorinated C_1-C_4 alkyl, fluorinated C_1-C_4 alkoxy, C_1-C_4 alkylsulfonyl, C_1-C_4 alkylcarbonyl, cyano, aryl, heteroaryl, arC_1-C_4 alkyl, C_2-C_4 alkenyl, alkynyl, or nitro;

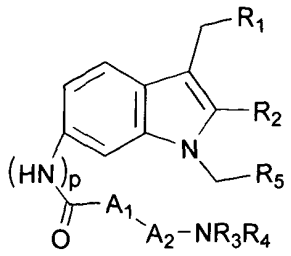
R_2 is selected from hydrogen, chlorine or phenyl;

R_3 is selected from hydrogen or C_1-C_4 alkyl; and

m and n are both 1;

and pharmaceutically acceptable salts thereof.

4. The compound of Claim 3 of the formula:



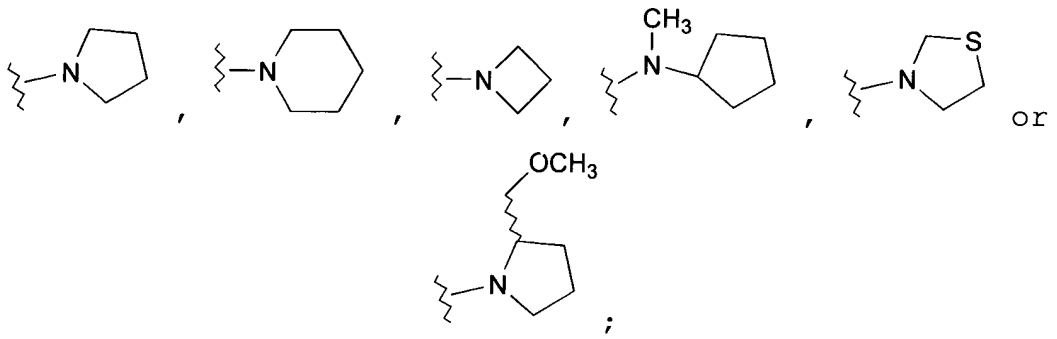
wherein:

A_1 is an L-amino acid selected from the group consisting of alanine, arginine, cyclohexylalanine, proline, tetrahydroisoquinoline-3-COOH, and an unsubstituted or substituted aromatic amino acid selected from the group consisting of phenylalanine, naphthylalanine, homophenylalanine, and O-methyl tyrosine, wherein the substituents on the aromatic amino acid are independently one to two substituents selected from halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, C_1-C_4 alkoxycarbonyl, amino, amidino, guanidino, fluorinated C_1-C_4 alkyl, fluorinated C_1-C_4 alkoxy, C_1-C_4 alkylsulfonyl, C_1-C_4 alkylcarbonyl, cyano, aryl, heteroaryl, arC_1-C_4 alkyl, C_2-C_4 alkenyl, alkynyl, or nitro;

A_2 is an L-amino acid selected from the group consisting of alanine, β-alanine, arginine, citrulline, cysteine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl), 2,4-diaminobutyric acid (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, amidino, or MeC(NH)-), 2,3-diaminopropionic acid (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, amidino, or MeC(NH)-), glutamine, glycine, lysine (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, MeC(NH)-), valine, methionine, serine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl), homoserine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl), threonine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl), ornithine (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, MeC(NH)-), and an unsubstituted or substituted aromatic amino acid selected from the group consisting of phenylalanine, heteroarylalanine, and histidine, wherein the substituents on the aromatic amino acid are independently one to two substituents selected from halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, C_1-C_4 alkoxycarbonyl, amino,

amidino, guanidino, fluorinated C_1-C_4 alkyl, fluorinated C_1-C_4 alkoxy, C_1-C_4 alkylsulfonyl, C_1-C_4 alkylcarbonyl, cyano, aryl, heteroaryl, arC_1-C_4 alkyl, C_2-C_4 alkenyl, alkynyl, or nitro;

R_1 is selected from diethylamino, di-(*n*-propyl)amino,



;

R_3 is selected from hydrogen, methyl or ethyl;

R_4 is selected from 2-indanyl, phenyl, cyclohexylmethyl, cyclopentyl, pyridylmethyl, furanylmethyl, 2-(4-methyl-furanyl)methyl, thienylmethyl, diphenylmethyl, 4-imidazolylethyl, 2-(4-N-methyl)imidazolylethyl, *n*-octyl, phenyl-*n*-propyl, aminoethyl, aminopropyl, amino-*n*-pentyl, dimethylaminoethyl, 4-aminophenylsulfonylaminomethyl, acetamidineylethyl, 2-N-pyrrolidinylethyl, N-ethoxycarbonylpiperidinyl, unsubstituted or substituted phenylethyl and unsubstituted or substituted benzyl wherein the substituents on the phenylethyl or benzyl are independently one or two substituents selected from methyl, fluorine, chlorine, nitro, methoxy, methoxycarbonyl or hydroxymethyl; or

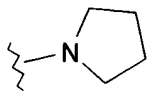
R_3 and R_4, together with the nitrogen to which they are attached, alternatively form a heteroalkyl group selected from piperidinyl or 4-(N-methyl)piperazinyl; and

R_5 is selected from cyclohexyl, 2-naphthyl, phenylethyl, 4-fluorophenylethyl, or unsubstituted or substituted phenyl, where the substituents on the phenyl are independently

selected from one to two substituents selected from fluorine, chlorine, iodine, methyl, cyano or trifluoromethyl;

and pharmaceutically acceptable salts thereof.

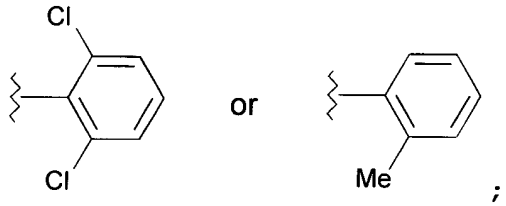
5. The compound of Claim 4, wherein:

R_1 is 

;

and pharmaceutically acceptable salts thereof.

6. The compound of Claim 5, wherein:

R_5 is selected from 

;

and pharmaceutically acceptable salts thereof.

7. The compound of Claim 6, wherein:

A_1 is selected from 3,4-Difluorophenylalanine or 4-Chlorophenylalanine;

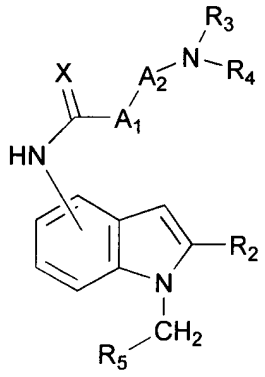
A_2 is selected from 2,4-Diaminobutyric acid or 4-Pyridylalanine;

R_3 is hydrogen; and

R_4 is selected from benzyl or 2-aminoethyl;

and pharmaceutically acceptable salts thereof.

8. A compound of the formula (II):



(II)

wherein:

A_1 and A_2 are each independently a D- or L-amino acid selected from the group consisting of alanine, β-alanine, arginine, homoarginine, cyclohexylalanine, citrulline, cysteine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl), 2,4-diaminobutyric acid (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, amidino, or MeC(NH)-), 2,3-diaminopropionic acid (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, amidino, or MeC(NH)-), glutamine, glycine, indanylglycine, lysine (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, MeC(NH)-), valine, methionine, proline, serine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl), homoserine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl), tetrahydroisoquinoline-3-COOH, threonine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl), ornithine (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, MeC(NH)-), and an unsubstituted or substituted aromatic amino acid selected from the group consisting of phenylalanine, heteroarylalanine, naphthylalanine, homophenylalanine, histidine, tryptophan, tyrosine, arylglycine, heteroarylglycine, aryl-β-alanine, and heteroaryl-β-alanine, wherein the substituents on the aromatic amino acid are independently selected from one or more of halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, C_1-C_4 alkoxycarbonyl, amino, amidino, guanidino,

fluorinated C_1-C_4 alkyl, fluorinated C_1-C_4 alkoxy, C_1-C_4 alkylsulfonyl, C_1-C_4 alkylcarbonyl, cyano, aryl, heteroaryl, arC_1-C_4 alkyl, C_2-C_4 alkenyl, alkynyl, or nitro;

R_2 is selected from hydrogen, halogen, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkenyl, C_1-C_8 alkynyl, arC_1-C_8 alkyl, aryl or heteroaryl;

R_3 and R_4 are each independently selected from hydrogen, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkylC_1-C_8 alkyl, aryl, heteroalkyl, substituted heteroalkyl (wherein the substituent on the heteroalkyl is one or more substituents independently selected from C_1-C_8 alkoxycarbonyl, C_1-C_8 alkyl, or C_1-C_4 alkylcarbonyl), heteroalkylC_1-C_8 alkyl, indanyl, acetamidinoC_1-C_8 alkyl, aminoC_1-C_8 alkyl, C_1-C_8 alkylaminoC_1-C_8 alkyl, C_1-C_8 dialkylaminoC_1-C_8 alkyl, unsubstituted or substituted heteroarylC_1-C_8 alkyl, or unsubstituted or substituted arC_1-C_8 alkyl, wherein the substituent on the aralkyl or heteroarylalkyl group is one or more substituents independently selected from halogen, nitro, amino, C_1-C_8 alkyl, C_1-C_8 alkoxy, hydroxy, cyano, C_1-C_4 alkylcarbonyl, C_1-C_8 alkoxycarbonyl, hydroxyC_1-C_8 alkyl or aminosulfonyl; or

R_3 and R_4, together with the nitrogen to which they are attached, alternatively form an unsubstituted or substituted heteroalkyl group selected from piperidinyl, piperazinyl, morpholinyl or pyrrolidinyl, wherein the substituent is one or more substituents selected from C_1-C_8 alkyl C_1-C_8 alkoxycarbonyl or C_1-C_4 alkylcarbonyl;

R_5 is selected from unsubstituted or substituted aryl, arC_1-C_8 alkyl, C_3-C_8 cycloalkyl, or heteroaryl, where the substituents on the aryl, arC_1-C_8 alkyl, cycloalkyl or heteroaryl group are independently selected from one or more of halogen, nitro, amino, cyano, hydroxyalkyl, C_1-C_8 alkyl, C_1-C_8 alkoxy, hydroxy, C_1-C_4 alkylcarbonyl, C_1-C_8 alkoxycarbonyl, fluorinated C_1-C_4 alkyl, fluorinated C_1-C_4 alkoxy or C_1-C_4 alkylsulfonyl; and,

X is oxygen or sulfur; and salts thereof.

10. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of Claim 1.

11. A pharmaceutical composition made by mixing a compound of Claim 1 and a pharmaceutically acceptable carrier.

12. A process for making a pharmaceutical composition comprising mixing a compound of Claim 1 and a pharmaceutically acceptable carrier.

ORT-1236

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Zhang et al.

Serial No.: 09/603,231 Art Unit: 1634

Filed : June 26, 2000 Examiner: Chakrabarti, Arun K.

For : NOVEL INDOLE PEPTIDOMIMETICS AS THROMBIN RECEPTOR ANTAGONISTS

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Mail Stop Appeal Brief - Patents, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on

August 26, 2003
(Date of Deposit)

Hal B. Woodrow
(Name of applicant, assignee, or Registered Representative)

Hal Burt Woodrow
(Signature)

August 26, 2003
(Date of Signature)

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPELLANT'S BRIEF

Appellants respectfully request the Board of Patent Appeals and Interferences reverse the Final Rejection of claims 1-8, 10 and 11 and direct the allowance of said claims.

1. Real Party in Interest

The real party in interest is the assignee, Ortho-McNeil Pharmaceutical, Inc., a Delaware corporation, (and subsidiary of Johnson & Johnson) and COR Therapeutics Inc. (which has been acquired by Millennium Pharmaceutical).

2. Related Appeals and Interferences

There are no related appeals or interferences.

3. Status of the Claims

Claims 1-24 were original present. Claims 9 and 12-24 were subject to a restriction requirement and withdrawn from consideration. Pending claim 1-8 and 10-11 and were finally rejected in the Office Action dated September 20, 2002. Claims have been finally rejected under 35 U.S.C. § 103 as being unpatentable over Forbes (WO 93/18026) and Hoekstra (U.S. Patent 6,017,890).

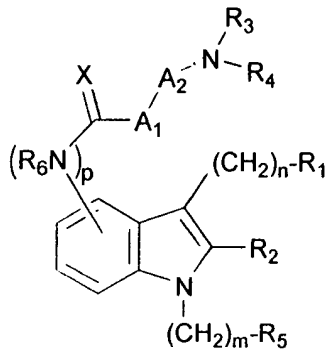
4. Status of Amendments

The first Amendment submitted after Final Rejection was considered. See Advisory Action of April 8, 2003.

5. Summary of the Invention

The invention that is being claimed is a compound of the formula (I).

1. A compound of the following formula (I):



(I)

wherein:

A_1 and A_2 are each independently a D- or L-amino acid selected from the group consisting of alanine, β-alanine, arginine, homoarginine, cyclohexylalanine, citrulline, cysteine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl), 2,4-diaminobutyric acid (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, amidino, or MeC(NH)-), 2,3-diaminopropionic acid (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, amidino, or MeC(NH)-), glutamine, glycine, indanylglycine, lysine (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, MeC(NH)-), valine, methionine, proline, serine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl), homoserine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl), tetrahydroisoquinoline-3-COOH, threonine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl), ornithine (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, MeC(NH)-), and an unsubstituted or substituted aromatic amino acid selected from the group consisting of phenylalanine, heteroarylalanine, naphthylalanine, homophenylalanine, histidine, tryptophan, tyrosine, arylglycine, heteroarylglycine, aryl-β-alanine, and heteroaryl-β-alanine wherein the substituents on the aromatic amino acid are independently selected from one or more of halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, C_1-C_4 alkoxycarbonyl, amino, amidino, guanidino,

fluorinated C_1-C_4 alkyl, fluorinated C_1-C_4 alkoxy, C_1-C_4 alkylsulfonyl, C_1-C_4 alkylcarbonyl, cyano, aryl, heteroaryl, arC_1-C_4 alkyl, C_2-C_4 alkenyl, alkynyl, or nitro;

R_1 is selected from amino, C_1-C_8 alkylamino, C_1-C_8 dialkylamino, arylamino, arC_1-C_8 alkylamino, C_3-C_8 cycloalkylamino, heteroalkylC_1-C_8 alkylamino, heteroalkylC_1-C_8 alkyl-N-methylamino, C_1-C_8 dialkylaminoC_1-C_8 alkylamino, -N(C_1-C_8alkyl)-C_1-C_8 alkyl-N(C_1-C_8alkyl)$_2$, N(C_1-C_8 alkyl)(C_1-C_8 alkenyl), -N(C_1-C_8alkyl)(C_3-C_8cycloalkyl), heteroalkyl or substituted heteroalkyl wherein the substituent on the heteroalkyl is selected from oxo, amino, C_1-C_8 alkoxyC_1-C_8 alkyl, C_1-C_8 alkylamino or C_1-C_8 dialkylamino;

R_2 is selected from hydrogen, halogen, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkenyl, C_1-C_8 alkynyl, arC_1-C_8 alkyl, aryl or heteroaryl;

R_3 and R_4 are each independently selected from hydrogen, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkylC_1-C_8 alkyl, aryl, heteroalkyl, substituted heteroalkyl (wherein the substituent on the heteroalkyl is one or more substituents independently selected from C_1-C_8 alkoxycarbonyl, C_1-C_8 alkyl, or C_1-C_4 alkylcarbonyl), heteroalkylC_1-C_8 alkyl, indanyl, acetamidinoC_1-C_8 alkyl, aminoC_1-C_8 alkyl, C_1-C_8 alkylaminoC_1-C_8 alkyl, C_1-C_8 dialkylaminoC_1-C_8 alkyl, unsubstituted or substituted heteroarylC_1-C_8 alkyl, or unsubstituted or substituted arC_1-C_8 alkyl, wherein the substituent on the aralkyl or heteroarylalkyl group is one or more substituents independently selected from halogen, nitro, amino, C_1-C_8 alkyl, C_1-C_8 alkoxy, hydroxy, cyano, C_1-C_4 alkylcarbonyl, C_1-C_8 alkoxycarbonyl, hydroxyC_1-C_8 alkyl or aminosulfonyl; or

R_3 and R_4, together with the nitrogen to which they are attached, alternatively form an unsubstituted or substituted heteroalkyl group selected from piperidinyl, piperazinyl, morpholinyl or pyrrolidinyl, wherein the substituent is one or more substituents independently selected from C_1-C_8 alkyl C_1-C_8 alkoxycarbonyl or C_1-C_4 alkylcarbonyl;

R_5 is selected from unsubstituted or substituted aryl, arC_1-C_8 alkyl, C_3-C_8 cycloalkyl, or heteroaryl, where the substituents on the aryl, arC_1-C_8 alkyl, cycloalkyl or heteroaryl group are independently selected from one or more of halogen, nitro, amino, cyano, hydroxyalkyl, C_1-C_8 alkyl, C_1-C_8 alkoxy, hydroxy, C_1-C_4 alkylcarbonyl, C_1-C_8 alkoxycarbonyl, fluorinated C_1-C_4 alkyl, fluorinated C_1-C_4 alkoxy or C_1-C_4 alkylsulfonyl;

R_6 is selected from hydrogen or C_1-C_8 alkyl,

X is oxygen or sulfur;

m is an integer selected from 0, 1, 2 or 3;
n is an integer selected from 1 or 2; and
p is an integer selected from 0 or 1;

and pharmaceutically acceptable salts thereof.

6. Issues

I. Whether a prima facie case of obviousness has been established for the rejection of claims 1-8, 10 and 11 under 35 U.S.C. §103.

II. Whether a case of structural obviousness has been established for the rejection of claims 1-8, 10 and 11 under 35 U.S.C. § 103.

7. Grouping of the Claims

For Issue I, claims 1-8, 10 and 11 shall stand or fall together.

For Issue II, claims 1-8, 10 and 11 shall stand or fall together.

8. Arguments

I

The rejection of claims 1-8, 10 and 11 under 35 U.S.C. 103 (a) over Forbes et al. over Hoekstra et al. is submitted to be in error for the reasons argued here in (paraphrasing In re Dembiczak 50 USPQ 1614 (Fed. Cir. 1999)).

'A claimed invention is unpatentable if the differences between it and the prior art "are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a) (Supp. 1998); see Graham v. John Deere Co., 383 U.S. 1, 14, 148 USPQ 459, 465 (1966). The ultimate determination of whether an invention is or is not obvious is a legal conclusion based on underlying factual inquiries including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the prior art; (3) the differences between the claimed invention and the prior art; and (4) objective evidence of nonobviousness. See Graham, 383 U.S. at 17-18, 148 USPQ at 467; Miles Labs, Inc., Inc. v. Shandon Inc., 997 F.2d 870, 877, 27 USPQ2d 1123, 1128 (Fed. Cir. 1993).

The analysis of obviousness must begin with the text of section 103 quoted above, with the phrase "at the time the invention was made." For it is this phrase that guards against entry into the "tempting but forbidden zone of hindsight," see Loctite Corp. v. Ultraseal Ltd., 781 F.2d 861, 873, 228 USPQ 90, 98 (Fed. Cir. 1985), overruled on other grounds by Nobelpharma AB v. Implant Innovations, Inc., 141 F.3d 1059, 46 USPQ2d 1097 (Fed. Cir. 1998), when analyzing the patentability of claims pursuant to that section. Measuring a claimed invention against the standard established by section 103 requires the oft-difficult but critical step of casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided

only by the prior art references and the then-accepted wisdom in the field. See, e.g., W.L. Gore & Assoc., Inc. v. Garlock, Inc., 721 F.2d 1540, 1553, 220 UPSQ 303, 313 (Fed. Cir. 1983).

The Federal Circuit's case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references. See, e.g., C.R. Bard, Inc. v. M3 Sys., Inc., 157 F.3d 1340, 1352, 48 USPQ2d 1225, 1232 (Fed. Cir. 1998) (describing "teaching or suggestion or motivation [to combine]" as an "essential evidentiary component of an obviousness holding"); In re Rouffet, 149 F.3d 1350, 1359, 47 USPQ2d 1453, 1459 (Fed. Cir. 1998) ("the Board must identify specifically . . . the reasons one of ordinary skill in the art would have been motivated to select the references and combine them"); In re Fritch, 972 F.2d 1260, 1265, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992) (examiner can satisfy burden of obviousness in light of combination "only by showing some objective teaching [leading to the combination]"); In re Fine, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988) (evidence of teaching or suggestion "essential" to avoid hindsight); Ashland Oil, Inc. v. Delta Resins & Refractories, Inc., 776 F.2d 281, 297, 227 USPQ 657, 667 (Fed. Cir. 1985) (district court's conclusion of obviousness was error when it "did not elucidate any factual teachings, suggestions or incentives from this prior art that showed the propriety of combination"). See also Graham, 383 U.S. at 18, 148 USPQ at 467 ("strict observance" of factual predicates to obviousness conclusion required). Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight. See, e.g., Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1138, 227 USPQ 543, 547 (Fed. Cir. 1985) ("The invention must be viewed not with the blueprint drawn by the inventor, but in the state of the art that existed at the time."). In this case, it appears that the Examiner has fallen into the hindsight trap.'

Forbes et al. on page 1 of the specification in lines 13 et seq. describes the application as being a new class of compounds that have been found to have $5HT_{1C}$ receptor antagonist activity. $5HT_{1C}$ receptors antagonists are described in Forbes as being potential use for the treatment of CNS disorders such as anxiety, depression, obsessive compulsive disorders, migraine, anorexia, Alzheimers disease, sleep disorders, bulimia, panic attacks, withdrawal from drug abuse and/or schizophrenia. 5-HT1C (5-hydroxytryptamine) is a G protein-coupled serotonin receptor. The $5HT_{1C}$ receptor according to Pompeiano et al. (abstract provided to the examiner) indicates that $5HT_{1C}$ has been renamed the 5-HT2C receptor. The potential medical benefits of 5-HT research is described by Jones et al. (article provided to the examiner). Jones suggests that selective 5HT2C receptor antagonists could have antidepressant properties (see page 557), a role in the treatment of generalized anxiety disorder (page 559) and appetite (page 563).

Forbes et al. does not teach, suggest or disclose that there are any similarity between compounds that would antagonize the 5HT2C receptor and compounds that would antagonize the PAR-1 receptors. There does not appear to be any suggestion or disclosure in Forbes et al. that the compounds described therein have any activity toward the PAR-1 receptor. Forbes also does not suggest or describe modifying the compounds described therein to make the compounds that are claimed by the applicants.

Although Hoekstra et al. is a significant contribution to the art of PAR-1 antagonists, Hoekstra does not teach, suggest or disclose that the compounds described therein are 5HT2C antagonists. Hoekstra et al. also does not teach, suggest or disclose compounds of the structure being claimed in the present invention. Hoekstra et al. also does not teach or suggest that the A1 and A2 portion of the compounds that he claims may be combined with other scaffolds such as those described by Forbes et al. to provide PAR1 antagonists.

The Examiner has asserted that Hoekstra et al. "teach a compound with A1 and A2 which are D- or L- amino acids" in (Column 1, lines 8-35 and Claim 1). See Advisory Action page 2, third paragraph. However, Hoekstra et al. in Column 1, lines 8-35 discusses prior art publications

related to SFLLRN (Ser-Phe-Leu-Leu-Arg-Asn) a six amino acid motif that is involved in PAR1 receptor activation. Claim 1 of Hoekstra et al. defines a chemical structure that is a PAR1 antagonist. Neither the prior art nor Hoekstra suggest or disclose that A1 and A2 can be selectively removed from the SFLLRN motif or the compound of claim 1 and combined with other structures to provide a PAR1 antagonist.

In view of the deficiencies in Forbes et al. and Hoekstra et al., appellants respectfully submit that one of ordinary skill in the art when designing a PAR-1 antagonist would not be motivated to combine part of Forbes 5HT2C compounds with part of Hoekstra's disclosed compounds to form the claimed invention. The documents of record simply do not evidence a suggestion, teaching, or motivation to combine the documents of record. See In re Fine, 837 F.2d 1071, 5 USPQ2d 1596, (Fed. Cir. 1988). There must be a clear and particular showing of this evidence. See, e.g., C.R. Bard, 157 F.3d at 1352, 48 USPQ2d at 1232. Conclusory statements regarding the teaching of multiple references, standing alone, is not "evidence." E.g., McElmurry v. Arkansas Power & Light Co., 995 F.2d 1576, 1578, 27 USPQ2d 1129, 1131 (Fed. Cir. 1993). Therefore, appellants respectfully submit that the Office has not met its burden of establishing a *prima facie* case of obviousness.

The present rejection of the claims is limited to a discussion of the ways that the prior art references can be combined to read on the claimed invention. Yet this analysis fails to demonstrate how the Forbes et al. and Hoekstra et al. references teach or suggest their combination to yield the claimed invention. See Rouffet, 149 F.3d at 1357, 47 USPQ2d at 1459. Appellants respectfully submit that they do not discern any suggestion, teaching, or motivation to combine the prior art references cited against the pending claims. Therefore appellants respectfully submit that the Examiner's conclusion that the present claims are obviousness, as a matter of law, cannot stand. See C.R. Bard, 157 F.3d at 1352, 48 USPQ2d at 1232; Rouffet, 149 F.3d at 1359, 47 USPQ2d at 1459; Fritch, 972 F.2d at 1265, 23 USPQ2d at 1783; Fine, 837 F.2d at 1075, 5 USPQ2d at 1600; Ashland Oil, 776 F.2d at 297, 227 USPQ at 667. Appellants note

the Examiner's citation of In re McLaughlin, 443 F.2d 1392, 170 USPQ 209, however, appellants do not believe the selective hindsight evidenced in the present rejection would pass the test set forth in current case law.

Accordingly appellants respectfully submit that the rejection of claims 1-8, 10 and 11 under 35 U.S.C. 103 (a) over Forbes et al. over Hoekstra et al. is in error and should be reversed.

II

Claims 1-8, 10 and 11 have been rejected under 35 U.S.C. 103 (a) over Forbes et al. and Hoekstra et al. However, appellants respectfully submit that a *prima facie* case of structural obviousness has not been established by the Forbes et al. or Hoekstra et al. taken alone or together.

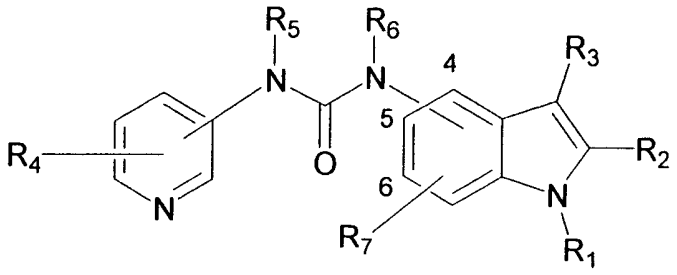
A claimed invention is unpatentable if the differences between it and the prior art "are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a) (Supp. 1998); see Graham v. John Deere Co., 383 U.S. 1, 14, 148 USPQ 459, 465 (1966). The ultimate determination of whether an invention is or is not obvious is a legal conclusion based on underlying factual inquiries including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the prior art; (3) the differences between the claimed invention and the prior art; and (4) objective evidence of nonobviousness. See Graham, 383 U.S. at 17-18, 148 USPQ at 467; Miles Labs, Inc., Inc. v. Shandon Inc., 997 F.2d 870, 877, 27 USPQ2d 1123, 1128 (Fed. Cir. 1993).

In Yamanouchi Pharmaceutical v Merck, 231 F.3d 1339, 1343 56 U.S.P.Q.2d 1641 (Fed. Cir. 2000), reh'g and reh'g en banc denied, (Dec. 14, 2000) the Federal Circuit explained the obviousness standard for chemical compounds as follows:

For a chemical compound, a prima facie case of obviousness requires "structural similarity between claimed and prior art subject matter . . . where the prior art gives reason or motivation to make the claimed compositions." In re Dillon, 919 F.2d 688, 692, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990) (en banc). "[A] reasonable expectation of success, not absolute predictability" supports a conclusion of obviousness. In re Longi, 759 F.2d 887, 896, 225 USPQ 645, 651-52 (Fed. Cir. 1985).

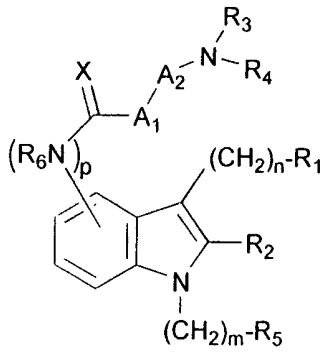
There must be motivation to combine the prior art references to produce the claimed invention. The question in the Yamanouchi dispute was whether one of skill in the art would have found the motivation to combine pieces from one compound in a prior art patent with a piece of another compound in a second prior art patent through a series of manipulations. In Yamanouchi as here the assertion of obviousness was based on a combination of pieces of other compounds followed by further modifications to provide the final compound. The Court set forth three specific requirements that would have to be met for structural obviousness to be proven. First the prior art would have to provide the specific motivation to combine the references (which is lacking here). Second the Court went on to indicate that a reasonable expectation of success in finding active would also have to be expected of the claimed compounds by one of ordinary skill in the art (which does not appear to be present here). Third the Court indicated that the prior art must offer a suggestion to pursue the particular manipulation of parts of the compounds (which also does not exist here).

Assuming for the purpose of this discussion only that Forbes et al. could be properly combined with Hoekstra et al., the rejection of the claimed invention over Forbes et al. over Hoekstra et al. does not satisfy the test for obviousness set forth in Yamanouchi. The Advisory Action has alleged that Forbes et al. Formula I teaches all the limitation of claims 1-8, but devoid of A1 and A2. However, this statement is factually incorrect. Forbes et al. shows a pyridine linked through a urea to an indole in Formula (I).



Formula (I) of Forbes et al.

That structure does not exist in claim 1-8. The appellants' claimed compounds do not provide the same urea pyridine structure.



(Formula I of Appellants' Claimed Compounds)

Thus, Forbes et al. does not meet all the limitations of claims 1-8. Consequently, the addition of A1 and A2 of Hoekstra et al. to Forbes et al. does not provide the compounds of claims 1-8.

Even if one were to ignore the additional pyridine present in Forbes et al., the structure described by Forbes as his pharmaceutically active compound on pages 1 and 2 of the specification still would not provide the same compounds as are being claimed by the appellants. Forbes shows the indole portion of his compound as being substituted with R_1, R_2, and R_3. These substituents are described as hydrogen or C_{1-6} alkyl on page 2, line 1 of Forbes et al. The appellants' claimed compounds on the indole ring claims 1-8 define different substituents being

substituted from the indole ring. For example, R_1 of Forbes et al. corresponds to $(CH_2)_m$-R_5 of the appellants' compound which is defined as:

In claim 1:

R_5 is selected from unsubstituted or substituted aryl, arC_1-C_8 alkyl, C_3-C_8 cycloalkyl, or heteroaryl, where the substituents on the aryl, arC_1-C_8 alkyl, cycloalkyl or heteroaryl group are independently selected from one or more of halogen, nitro, amino, cyano, hydroxyalkyl, C_1-C_8 alkyl, C_1-C_8 alkoxy, hydroxy, C_1-C_4 alkylcarbonyl, C_1-C_8 alkoxycarbonyl, fluorinated C_1-C_4 alkyl, fluorinated C_1-C_4 alkoxy or C_1-C_4 alkylsulfonyl;

In claim 4:

R_5 is selected from cyclohexyl, 2-naphthyl, phenylethyl, 4-fluorophenylethyl, or unsubstituted or substituted phenyl, where the substituents on the phenyl are independently selected from one to two substituents selected from fluorine, chlorine, iodine, methyl, cyano or trifluoromethyl;

Similarly R_3 of Forbes corresponds to $(CH_2)_n$-R_1 of the appellants' compound which is defined to be

In claim 1:

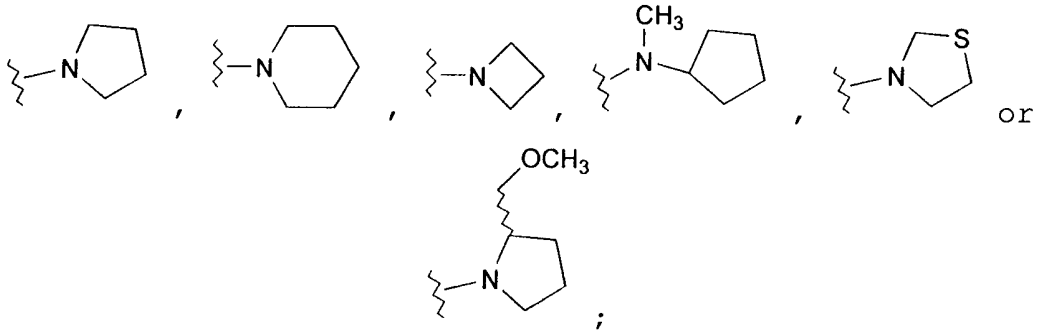
R_1 is selected from amino, C_1-C_8 alkylamino, C_1-C_8 dialkylamino, arylamino, arC_1-C_8 alkylamino, C_3-C_8 cycloalkylamino, heteroalkylC_1-C_8 alkylamino, heteroalkylC_1-C_8 alkyl-N-methylamino, C_1-C_8 dialkylaminoC_1-C_8 alkylamino, -N(C_1-C_8alkyl)-C_1-C_8 alkyl-N(C_1-C_8alkyl)$_2$, N(C_1-C_8 alkyl)(C_1-C_8 alkenyl), -N(C_1-C_8alkyl)(C_3-C_8cycloalkyl), heteroalkyl or substituted heteroalkyl wherein the substituent on the heteroalkyl is selected from oxo, amino, C_1-C_8 alkoxyC_1-C_8 alkyl, C_1-C_8 alkylamino or C_1-C_8 dialkylamino;

In claim 2:

R_1 is selected from amino, C_1-C_6 alkylamino, C_1-C_6 dialkylamino, arylamino, arC_1-C_6 alkylamino, heteroalkylC_1-C_6 alkylamino, -N(C_1-C_6 alkyl)-C_1-C_6 alkyl-N(C_1-C_6 alkyl)$_2$, heteroalkyl or substituted heteroalkyl wherein the substituent on the heteroalkyl is selected from oxo, amino, C_1-C_6 alkoxy C_1-C_6 alkyl, C_1-C_6 alkylamino or C_1-C_6 dialkylamino;

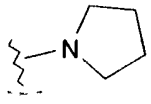
In claim 4:

R_1 is selected from diethylamino, di-(*n*-propyl)amino,



;

In claim 5:

R_1 is 

;

Following the tests set forth in Yamanouchi the first step of the analysis is to determine whether one of sill in the art would have been found motivation to combine the Forbes et al. and Hoekstra et al. references, which as was argued in Issue I is simply not present in the references. The second and third step of the Yamanouchi analysis are to determine whether there is a reasonable expectation of success in finding that activity and for performing the manipulations. As was previously argued, since the Forbes et al. reference is related to a totally different receptor the expectation of finding activity for the PAR1 receptor when combining selected portions of the

Forbes compound with selected portions of the Hoekstra compounds does not provide a reasonable expectation that a pharmaceutically active compound for the PAR1 receptor would be provided. The third step of the Yamanouchi analysis is to determine whether there is a suggestion to pursue the particular manipulation of parts of the compounds. In reviewing the combination Forbes et al and Hoekstra et al. as described above it is clear that the combination does not suggest or disclose the compounds that are being claimed. Therefore, the question is whether the references would suggest pursuing the particular manipulations of parts of the compounds to arrive at the claimed compounds. However, on inspection of Forbes et al. and Hoekstra et al. there is no motivation provided for the combination of these references much less for the modifications of Forbes et al. to remove the pyridine ring and modify the R group extending from the indole ring, nor the selection of A1 and A2 from Hoekstra to add to a modified Forbes compound.

Appellants have taken note that although the rejection has been stated to be based on formula (I) of Forbes et al., it has been suggested that formula IV of Forbes is also being applied against the claimed invention. For example, on page 6 of Paper 12 it is stated that with regard to R_1 and R_3 of Forbes, that the intermediates for R_1 and R_3 of indole portion of Forbes are being used in combination with Hoekstra as the basis of the rejection. To have structural obviousness as was stated in Yamanouchi, there must be a showing of motivation in the prior art for this combination, a reasonable expectation of success and a suggestion to pursue this particular manipulation (the use of an intermediate to form the final active compound). As applicants have previously discussed there is no basis for combining Forbes et al. and Hoekstra et al. Additionally, Forbes does not teach, suggest or disclose that the intermediate portion of the Forbes compound possesses activity. Appellants respectfully submit that one of ordinary skill in the art would not have been motivated to select an inactive intermediates of Forbes et al. compound to modify by the addition of the A1 and A2 components of Hoekstra et al. while removing the pyridine component of Forbes. Similarly one of ordinary skill in the art would not have had a reasonable expectation that such a compound so modified would have pharmaceutical activity. Consequently, appellants submit that the reasonable expectation of success is lacking here. Further, there is ***no basis*** for picking and choosing any

portion of Forbes et al. much less an intermediate of a portion of Forbes to piece together with portions of Hoekstra et al. in an attempt to recreate the present invention. There is also no teaching, suggestion or disclosure in Forbes or Hoekstra that would motivate this course of action. Therefore, appellants' submit that the rejection of claims 1-8, 10 and 11 does not meet the tests Yamanouchi and a *prima facie* case of structural obviousness has not been established for the claimed compound.

Accordingly appellants respectfully submit that the rejection of claims 1-8, 10 and 11 under 35 U.S.C. 103 (a) over Forbes et al. over Hoekstra et al. is in error and should be reversed.

Conclusion

In conclusion, appellants respectfully request that the Board of Patent Appeals and Interferences reverse the Final Rejection of claims 1-8, 10 and 11 over Forbes et al and Hoekstra et al. and direct the allowance of claims 1-8, 10 and 11.

Respectfully submitted,

Hal Brent Woodrow

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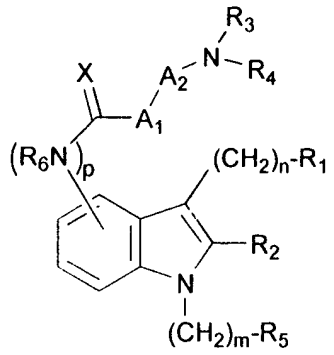
APPENDIX

WHAT IS CLAIMED IS:

1. A compound of the following formula (I):



(I)

wherein:

A_1 and A_2 are each independently a D- or L-amino acid selected from the group consisting of alanine, β-alanine, arginine, homoarginine, cyclohexylalanine, citrulline, cysteine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl), 2,4-diaminobutyric acid (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, amidino, or MeC(NH)-), 2,3-diaminopropionic acid (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, amidino, or MeC(NH)-), glutamine, glycine, indanylglycine, lysine (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, MeC(NH)-), valine, methionine, proline, serine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl), homoserine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl), tetrahydroisoquinoline-3-COOH, threonine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl), ornithine (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, MeC(NH)-), and an unsubstituted or substituted aromatic amino acid selected from the group consisting of

phenylalanine, heteroarylalanine, naphthylalanine, homophenylalanine, histidine, tryptophan, tyrosine, arylglycine, heteroarylglycine, aryl-β-alanine, and heteroaryl-β-alanine wherein the substituents on the aromatic amino acid are independently selected from one or more of halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, C_1-C_4 alkoxycarbonyl, amino, amidino, guanidino, fluorinated C_1-C_4 alkyl, fluorinated C_1-C_4 alkoxy, C_1-C_4 alkylsulfonyl, C_1-C_4 alkylcarbonyl, cyano, aryl, heteroaryl, arC_1-C_4 alkyl, C_2-C_4 alkenyl, alkynyl, or nitro;

R_1 is selected from amino, C_1-C_8 alkylamino, C_1-C_8 dialkylamino, arylamino, arC_1-C_8 alkylamino, C_3-C_8 cycloalkylamino, heteroalkylC_1-C_8 alkylamino, heteroalkylC_1-C_8 alkyl-N-methylamino, C_1-C_8 dialkylaminoC_1-C_8 alkylamino, -N(C_1-C_8alkyl)-C_1-C_8 alkyl-N(C_1-C_8alkyl)$_2$, N(C_1-C_8 alkyl)(C_1-C_8 alkenyl), -N(C_1-C_8alkyl)(C_3-C_8cycloalkyl), heteroalkyl or substituted heteroalkyl wherein the substituent on the heteroalkyl is selected from oxo, amino, C_1-C_8 alkoxyC_1-C_8 alkyl, C_1-C_8 alkylamino or C_1-C_8 dialkylamino;

R_2 is selected from hydrogen, halogen, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkenyl, C_1-C_8 alkynyl, arC_1-C_8 alkyl, aryl or heteroaryl;

R_3 and R_4 are each independently selected from hydrogen, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkylC_1-C_8 alkyl, aryl, heteroalkyl, substituted heteroalkyl (wherein the substituent on the heteroalkyl is one or more substituents independently selected from C_1-C_8 alkoxycarbonyl, C_1-C_8 alkyl, or C_1-C_4 alkylcarbonyl), heteroalkylC_1-C_8 alkyl, indanyl, acetamidinoC_1-C_8 alkyl, aminoC_1-C_8 alkyl, C_1-C_8 alkylaminoC_1-C_8 alkyl, C_1-C_8 dialkylaminoC_1-C_8 alkyl, unsubstituted or substituted heteroarylC_1-C_8 alkyl, or unsubstituted or substituted arC_1-C_8 alkyl, wherein the substituent on the aralkyl or heteroarylalkyl group is one or more substituents independently selected from halogen, nitro, amino, C_1-C_8 alkyl, C_1-C_8 alkoxy, hydroxy, cyano, C_1-C_4 alkylcarbonyl, C_1-C_8 alkoxycarbonyl, hydroxyC_1-C_8 alkyl or aminosulfonyl; or

R_3 and R_4, together with the nitrogen to which they are attached, alternatively form an unsubstituted or substituted heteroalkyl group selected from piperidinyl, piperazinyl, morpholinyl

or pyrrolidinyl, wherein the substituent is one or more substituents independently selected from C_1-C_8 alkyl C_1-C_8 alkoxycarbonyl or C_1-C_4 alkylcarbonyl;

R_5 is selected from unsubstituted or substituted aryl, arC_1-C_8 alkyl, C_3-C_8 cycloalkyl, or heteroaryl, where the substituents on the aryl, arC_1-C_8 alkyl, cycloalkyl or heteroaryl group are independently selected from one or more of halogen, nitro, amino, cyano, hydroxyalkyl, C_1-C_8 alkyl, C_1-C_8 alkoxy, hydroxy, C_1-C_4 alkylcarbonyl, C_1-C_8 alkoxycarbonyl, fluorinated C_1-C_4 alkyl, fluorinated C_1-C_4 alkoxy or C_1-C_4 alkylsulfonyl;

R_6 is selected from hydrogen or C_1-C_8 alkyl,

X is oxygen or sulfur;

m is an integer selected from 0, 1, 2 or 3;
n is an integer selected from 1 or 2; and
p is an integer selected from 0 or 1;

and pharmaceutically acceptable salts thereof.

2. The compound of Claim 1, wherein:

A_1 and A_2 are each independently an L-amino acid selected from the group consisting of alanine, β-alanine, arginine, homoarginine, cyclohexylalanine, citrulline, cysteine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl), 2,4-diaminobutyric acid (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, amidino, or MeC(NH)-), 2,3-diaminopropionic acid (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, amidino, or MeC(NH)-), glutamine, glycine, indanylglycine lysine (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, MeC(NH)-), valine, methionine, proline, serine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl), homoserine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl),

tetrahydroisoquinoline-3-COOH, threonine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl), ornithine (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, MeC(NH)-), and an unsubstituted or substituted aromatic amino acid selected from the group consisting of phenylalanine, heteroarylalanine, naphthylalanine, homophenylalanine, histidine, tryptophan, tyrosine, arylglycine, heteroarylglycine, aryl-β-alanine, and heteroaryl-β-alanine wherein the substituents on the aromatic amino acid are independently selected from one or more of halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, C_1-C_4 alkoxycarbonyl, amino, amidino, guanidino, fluorinated C_1-C_4 alkyl, fluorinated C_1-C_4 alkoxy, C_1-C_4 alkylsulfonyl, C_1-C_4 alkylcarbonyl, cyano, aryl, heteroaryl, arC_1-C_4 alkyl, C_2-C_4 alkenyl, alkynyl, or nitro;

R_1 is selected from amino, C_1-C_6 alkylamino, C_1-C_6 dialkylamino, arylamino, arC_1-C_6 alkylamino, heteroalkylC_1-C_6 alkylamino, -N(C_1-C_6 alkyl)-C_1-C_6 alkyl-N(C_1-C_6 alkyl)$_2$, heteroalkyl or substituted heteroalkyl wherein the substituent on the heteroalkyl is selected from oxo, amino, C_1-C_6 alkoxy C_1-C_6 alkyl, C_1-C_6 alkylamino or C_1-C_6 dialkylamino;

R_2 is selected from hydrogen, halogen or phenyl;

R_3 is selected from hydrogen or C_1-C_6 alkyl;

R_4 is selected from C_1-C_8 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkylC_1-C_6 alkyl, aryl, heteroarylC_1-C_6 alkyl, substituted heteroarylC_1-C_6 alkyl wherein the substituent is C_1-C_4 alkyl, heteroalkyl, heteroalkylC_1-C_6 alkyl, indanyl, acetamidinoC_1-C_6 alkyl, aminoC_1-C_6 alkyl, C_1-C_6 alkylaminoC_1-C_6 alkyl, C_1-C_6 dialkylaminoC_1-C_6 alkyl, arC_1-C_8 alkyl, substituted arC_1-C_8 alkyl wherein the substituent on the aralkyl group is one to five substituents independently selected from halogen, nitro, amino, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxycarbonyl, hydroxyalkyl or aminosulfonyl; or

R_3 and R_4, together with the nitrogen to which they are attached, alternatively form an unsubstituted or substituted heteroalkyl group selected from piperidinyl, piperazinyl or

pyrrolidinyl, wherein the substituent is independently one or two substituents selected from C_1-C_6 alkyl;

R_5 is selected from unsubstituted or substituted aryl, arC_1-C_6 alkyl, C_3-C_6 cycloalkyl or heteroaryl, where the substituents on the aryl, aralkyl, cycloalkyl or heteroaryl group are independently selected from one to three substituents selected from halogen, cyano, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 alkoxycarbonyl, fluorinated C_1-C_4 alkyl, fluorinated C_1-C_4 alkoxy or C_1-C_4 alkylsulfonyl;

R_6 is hydrogen; and

X is oxygen; and

p is 1;

and pharmaceutically acceptable salts thereof.

3. The compound of Claim 2, wherein:

A_1 is an L-amino acid selected from the group consisting of alanine, arginine, cyclohexylalanine, glycine, proline, tetrahydroisoquinoline-3-COOH, and an unsubstituted or substituted aromatic amino acid selected from the group consisting of phenylalanine, naphthylalanine, homophenylalanine, and O-methyl tyrosine, wherein the substituents on the aromatic amino acid are independently one to five substituents selected from halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, C_1-C_4 alkoxycarbonyl, amino, amidino, guanidino, fluorinated C_1-C_4 alkyl, fluorinated C_1-C_4 alkoxy, C_1-C_4 alkylsulfonyl, C_1-C_4 alkylcarbonyl, cyano, aryl, heteroaryl, arC_1-C_4 alkyl, C_2-C_4 alkenyl, alkynyl, or nitro;

A_2 is an L-amino acid selected from the group consisting of alanine, β-alanine, arginine, citrulline, cysteine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl), 2,4-diaminobutyric acid (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, amidino, or MeC(NH)-), 2,3- diaminopropionic acid (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, amidino, or MeC(NH)-), glutamine, glycine, lysine (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, MeC(NH)-), valine, methionine, serine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl), homoserine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl), threonine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl), ornithine (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, MeC(NH)-), and an unsubstituted or substituted aromatic amino acid selected from the group consisting of phenylalanine, heteroarylalanine, and histidine, wherein the substituents of the aromatic amino acid are independently one to five substituents selected from halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, C_1-C_4 alkoxycarbonyl, amino, amidino, guanidino, fluorinated C_1-C_4 alkyl, fluorinated C_1-C_4 alkoxy, C_1-C_4 alkylsulfonyl, C_1-C_4 alkylcarbonyl, cyano, aryl, heteroaryl, arC_1-C_4 alkyl, C_2-C_4 alkenyl, alkynyl, or nitro;

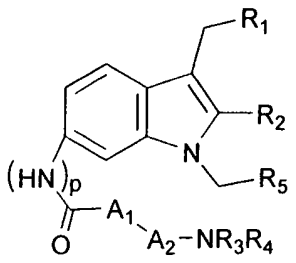
R_2 is selected from hydrogen, chlorine or phenyl;

R_3 is selected from hydrogen or C_1-C_4 alkyl; and

m and n are both 1;

and pharmaceutically acceptable salts thereof.

4. The compound of Claim 3 of the formula:



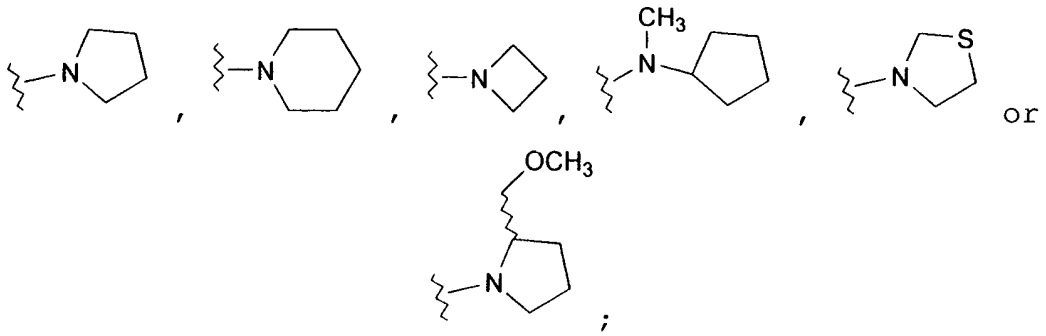
wherein:

A_1 is an L-amino acid selected from the group consisting of alanine, arginine, cyclohexylalanine, proline, tetrahydroisoquinoline-3-COOH, and an unsubstituted or substituted aromatic amino acid selected from the group consisting of phenylalanine, naphthylalanine, homophenylalanine, and O-methyl tyrosine, wherein the substituents on the aromatic amino acid are independently one to two substituents selected from halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, C_1-C_4 alkoxycarbonyl, amino, amidino, guanidino, fluorinated C_1-C_4 alkyl, fluorinated C_1-C_4 alkoxy, C_1-C_4 alkylsulfonyl, C_1-C_4 alkylcarbonyl, cyano, aryl, heteroaryl, arC_1-C_4 alkyl, C_2-C_4 alkenyl, alkynyl, or nitro;

A_2 is an L-amino acid selected from the group consisting of alanine, β-alanine, arginine, citrulline, cysteine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl), 2,4-diaminobutyric acid (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, amidino, or MeC(NH)-), 2,3-diaminopropionic acid (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, amidino, or MeC(NH)-), glutamine, glycine, lysine (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, MeC(NH)-), valine, methionine, serine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl), homoserine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl), threonine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl), ornithine (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, MeC(NH)-), and an unsubstituted or substituted aromatic amino acid selected from the group consisting of phenylalanine, heteroarylalanine, and histidine, wherein the substituents on the aromatic amino acid are independently one to two substituents selected from halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, C_1-C_4 alkoxycarbonyl, amino,

amidino, guanidino, fluorinated C_1-C_4 alkyl, fluorinated C_1-C_4 alkoxy, C_1-C_4 alkylsulfonyl, C_1-C_4 alkylcarbonyl, cyano, aryl, heteroaryl, arC_1-C_4 alkyl, C_2-C_4 alkenyl, alkynyl, or nitro;

R_1 is selected from diethylamino, di-(*n*-propyl)amino,



;

R_3 is selected from hydrogen, methyl or ethyl;

R_4 is selected from 2-indanyl, phenyl, cyclohexylmethyl, cyclopentyl, pyridylmethyl, furanylmethyl, 2-(4-methyl-furanyl)methyl, thienylmethyl, diphenylmethyl, 4-imidazolylethyl, 2-(4-N-methyl)imidazolylethyl, *n*-octyl, phenyl-*n*-propyl, aminoethyl, aminopropyl, amino-*n*-pentyl, dimethylaminoethyl, 4-aminophenylsulfonylaminomethyl, acetamidineylethyl, 2-N-pyrrolidinylethyl, N-ethoxycarbonylpiperidinyl, unsubstituted or substituted phenylethyl and unsubstituted or substituted benzyl wherein the substituents on the phenylethyl or benzyl are independently one or two substituents selected from methyl, fluorine, chlorine, nitro, methoxy, methoxycarbonyl or hydroxymethyl; or

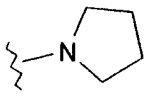
R_3 and R_4, together with the nitrogen to which they are attached, alternatively form a heteroalkyl group selected from piperidinyl or 4-(N-methyl)piperazinyl; and

R_5 is selected from cyclohexyl, 2-naphthyl, phenylethyl, 4-fluorophenylethyl, or unsubstituted or substituted phenyl, where the substituents on the phenyl are independently

selected from one to two substituents selected from fluorine, chlorine, iodine, methyl, cyano or trifluoromethyl;

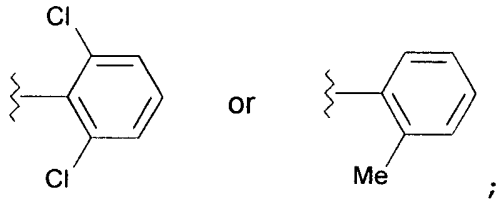
and pharmaceutically acceptable salts thereof.

5. The compound of Claim 4, wherein:

R_1 is  ;

and pharmaceutically acceptable salts thereof.

6. The compound of Claim 5, wherein:

R_5 is selected from  ;

and pharmaceutically acceptable salts thereof.

7. The compound of Claim 6, wherein:

A_1 is selected from 3,4-Difluorophenylalanine or 4-Chlorophenylalanine;

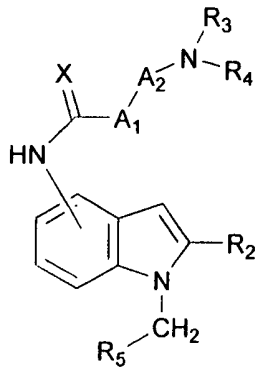
A_2 is selected from 2,4-Diaminobutyric acid or 4-Pyridylalanine;

R_3 is hydrogen; and

R_4 is selected from benzyl or 2-aminoethyl;

and pharmaceutically acceptable salts thereof.

8. A compound of the formula (II):



(II)

wherein:

A_1 and A_2 are each independently a D- or L-amino acid selected from the group consisting of alanine, β-alanine, arginine, homoarginine, cyclohexylalanine, citrulline, cysteine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl), 2,4-diaminobutyric acid (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, amidino, or MeC(NH)-), 2,3-diaminopropionic acid (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, amidino, or MeC(NH)-), glutamine, glycine, indanylglycine, lysine (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, MeC(NH)-), valine, methionine, proline, serine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl), homoserine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl), tetrahydroisoquinoline-3-COOH, threonine (optionally substituted with C_1-C_4 alkyl, aryl, or arC_1-C_4 alkyl), ornithine (optionally substituted with acyl, C_1-C_4 alkyl, aroyl, MeC(NH)-), and an unsubstituted or substituted aromatic amino acid selected from the group consisting of phenylalanine, heteroarylalanine, naphthylalanine, homophenylalanine, histidine, tryptophan, tyrosine, arylglycine, heteroarylglycine, aryl-β-alanine, and heteroaryl-β-alanine, wherein the substituents on the aromatic amino acid are independently selected from one or more of halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, C_1-C_4 alkoxycarbonyl, amino, amidino, guanidino,

fluorinated C_1-C_4 alkyl, fluorinated C_1-C_4 alkoxy, C_1-C_4 alkylsulfonyl, C_1-C_4 alkylcarbonyl, cyano, aryl, heteroaryl, arC_1-C_4 alkyl, C_2-C_4 alkenyl, alkynyl, or nitro;

R_2 is selected from hydrogen, halogen, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkenyl, C_1-C_8 alkynyl, arC_1-C_8 alkyl, aryl or heteroaryl;

R_3 and R_4 are each independently selected from hydrogen, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkylC_1-C_8 alkyl, aryl, heteroalkyl, substituted heteroalkyl (wherein the substituent on the heteroalkyl is one or more substituents independently selected from C_1-C_8 alkoxycarbonyl, C_1-C_8 alkyl, or C_1-C_4 alkylcarbonyl), heteroalkylC_1-C_8 alkyl, indanyl, acetamidinoC_1-C_8 alkyl, aminoC_1-C_8 alkyl, C_1-C_8 alkylaminoC_1-C_8 alkyl, C_1-C_8 dialkylaminoC_1-C_8 alkyl, unsubstituted or substituted heteroarylC_1-C_8 alkyl, or unsubstituted or substituted arC_1-C_8 alkyl, wherein the substituent on the aralkyl or heteroarylalkyl group is one or more substituents independently selected from halogen, nitro, amino, C_1-C_8 alkyl, C_1-C_8 alkoxy, hydroxy, cyano, C_1-C_4 alkylcarbonyl, C_1-C_8 alkoxycarbonyl, hydroxyC_1-C_8 alkyl or aminosulfonyl; or

R_3 and R_4, together with the nitrogen to which they are attached, alternatively form an unsubstituted or substituted heteroalkyl group selected from piperidinyl, piperazinyl, morpholinyl or pyrrolidinyl, wherein the substituent is one or more substituents selected from C_1-C_8 alkyl C_1-C_8 alkoxycarbonyl or C_1-C_4 alkylcarbonyl;

R_5 is selected from unsubstituted or substituted aryl, arC_1-C_8 alkyl, C_3-C_8 cycloalkyl, or heteroaryl, where the substituents on the aryl, arC_1-C_8 alkyl, cycloalkyl or heteroaryl group are independently selected from one or more of halogen, nitro, amino, cyano, hydroxyalkyl, C_1-C_8 alkyl, C_1-C_8 alkoxy, hydroxy, C_1-C_4 alkylcarbonyl, C_1-C_8 alkoxycarbonyl, fluorinated C_1-C_4 alkyl, fluorinated C_1-C_4 alkoxy or C_1-C_4 alkylsulfonyl; and,

X is oxygen or sulfur; and salts thereof.

10. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of Claim 1.

11. A pharmaceutical composition made by mixing a compound of Claim 1 and a pharmaceutically acceptable carrier.

12. A process for making a pharmaceutical composition comprising mixing a compound of Claim 1 and a pharmaceutically acceptable carrier.